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| 09/186,775 | 11/06/1998 | DIANE BURGESS | 012176-00621 | 2248 |

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TOWNSEND AND TOWNSEND AND CREW, LLP
TWO EMBARCADERO CENTER
EIGHTH FLOOR
SAN FRANCISCO, CA 94111-3834

| EXAMINER | |
|---|---|
| HELMER, GEORGIA L | |
| ART UNIT | PAPER NUMBER |
| 1638 | 19 |

DATE MAILED: 03/01/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. 09/186,775 | Applicant(s) BURGESS ET AL. | |
|---|---|---|---|
| | Examiner Cynthia Collins | Art Unit 1638 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *13 February 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-4,6,7,11-18,20,21 and 25-37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6,7,11-18,20,21 and 25-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

## DETAILED OFFICE ACTION

**09/186,775**

***Status of Claims***

1. The request filed on February 13, 2001 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/186,775 is acceptable and a CPA has been established. Claims 1 - 4, 6, 7, 11 – 18, 20, 21, and 25 – 37 are pending and are examined in the instant application.

2. The 1.132 declaration filed 2/13/01 with the CPA request has been considered. However, Applicant's arguments are deemed moot in light of the new grounds of rejection as set forth below.

***Claim Rejections - 35 USC § 112 second paragraph***

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-4, 6, 7, 11-18, 20, 21, and 25-37 are rejected as failing to particularly point out and distinctly claim the subject matter the applicant regards as his invention.

At claim 1, "each encodes a separate amino acid subsequence of a single functional nuclease" is indefinite because many different subsequences of a nuclease could be used without ever getting the single functional nuclease. Similar objection is made to all recitations of separate amino acid subsequence. What is missing here is the idea that the subsequences need to be complementary and when used together make the whole functional nuclease.

At claims 14, line 1, a method of "modifying cellular function" is indefinite because the metes and bounds of the claim are unclear. One could modify a large number of cellular functions in a myriad number of different ways and come up with potentially an infinite number of variations. It is suggested that claims be amended to recite -making a female-fertile male-sterile plant-.

At claim 14, lines 8-9, "and situated between the first promoter and the first polypeptide of the second" is unclear. It is suggested that the words -and situated between the first promoter and the first polynucleotide encoding the first polypeptide of the second- be inserted for clarification.

At claim 29, "overlapping specificities" is unclear. Are these specificities physically overlapping or are they overlapping in terms of their function or other attribute? Similar objection is made to all recitations of overlapping specificities.

Correction or clarification is required.

***Claim Rejections - 35 USC § 112 first paragraph***

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1 - 4, 6, 7, 11 – 18, 20, 21, and 25 – 37 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art

to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

5. Enablement is considered in view of the *Wands* factors (MPEP 2164.01(a)):

*Nature of the invention.* The claims are drawn to plant cells having at least two expression cassettes which when expressed in the same cell are lethal to the cell. And to methods of modifying plants which utilize plant cells having at least two expression cassettes which when expressed in the same cell are lethal to the cell. The claimed methods use site-specific recombination systems to modify gene expression.

*State of the prior art.* The state of the art is such that the skilled person can introduce a gene encoding a ribonuclease into a plant cell and express a single functional nuclease. However, the skilled person could not expect to express a single functional nuclease by introducing separate polynucleotides each encoding separate amino acid subsequences of a single functional ribonuclease. This is because many different subsequences of a nuclease could be used without ever getting the single functional nuclease. What is missing here is the idea that the polypeptide subsequences need to be complementary so that when used together in the same cell the whole functional nuclease is produced.

The art is such that the skilled person can introduce genes into plant cells but that generation of a given particular phenotype is unpredictable. Gene expression levels and inheritance are unpredictable (Deroles, SC and Gardner, RC; (1998) Plant Molecular Biology 11: 355-364 (X); Dunwell, JM and Paul, EM (1990) Outlook on Agriculture 19, 103-109 (W); Finnegan J and McElroy D (1994) Bio/Technology 12:

883-888)(V). Organ-specific gene expression in plants is variable (Van-der-Hoeven C et. al. (1994) Transgenic Research 3: 159-166)(U). Recombinase mediated excision of appropriately flanked DNA sequences is variable and yields chimeric phenotypes having both recombined and unrecombined DNA (Gidoni, D. et al, Supplement to Plant Molecular Biology Reporter 18:2, S 03-40; ISPMB abstracts, June 18-24, 2000)(U). Recent studies (Gidoni, D et al (2001) Euphytica 121: 145-156)(U) of embryonal recombination and germline inheritance of recombined tobacco loci show variable recombination efficiencies (Godini 2001, 146 and 152). The claimed methods require use of site-specific recombination systems to delete appropriately flanked DNA sequences.

*Breadth of the claims.* Claims are broadly drawn to modifying cellular functions in a plant. There exist a large number of cellular functions which could be modified in a myriad of different ways resulting in potentially an infinite number of variations. Recombinases and recombinase sites are encompassed broadly.

*Working examples.* There are no working examples.

*Guidance in the specification.* The specification contains three prophetic examples: Prophetic Example 1 (p 20) describes the use of a repressor/activator fusion protein to induce expression of barnase in tapetal cells. Prophetic Example 2 (pg 21) describes use of the AVR9 elicitor polypeptide from *Cladosporium fulvum* and the corresponding resistance gene Cf19 from *Lycopersicon esculentum* to specifically kill tapetal cells. Prophetic Example 3 (pg 22) describes the use of cre-lox system to insert

two functional expression cassettes into a lox site previously introduced into a plant genome.

Prophetic Example 1 discloses sequences of steps for the use of the cre/lox system to create alternative alleles at one locus. At several points in these steps (page 20, Example 1), which are illustrated in Figure1, Applicant directs "Pick best" or "PCR". However Applicant gives no guidance on criteria or methods for picking the best or the meaning of "PCR." Applicant does not provide guidance for which of the various genes/promoters/cassettes in conjunction with recombinases and/or recombinase target sites can be successfully deployed to create male-sterile plants of otherwise modify cellular functions. See discussion above re the state of the prior art.

Applicant's 1.132 Declaration filed 2/13/01 (Exhibit 2) gives detailed information on the production of a functional nuclease when complementary subsequences of the nuclease polypeptide are expressed in the same cell. This data is from experiments using a CaMV 35S promoter, which is a constitutive promoter. The Declaration also includes (pg 4, Exhibit 1) information on use of a tapetum specific promoter to produce complementary subsequences of nuclease polypeptides in the same cell.

The Declaration has no information or data on the use of recombinases, recombination target sites, repressor/activator fusion proteins to induce expression of barnase in tapetal cells, use of the AVR9 elicitor polypeptide from *Cladosporium fulvum* and the corresponding resistance gene Cf19 from *Lycopersicon esculentum* to specifically kill tapetal cells, or the use of cre-lox system to insert two functional expression cassettes into a lox site previously introduced into a plant genome

*Predictability of the art.* The physiological art in general is acknowledged to be unpredictable (MPEP 2164.03). Above discussions of predictability are repeated below:

The art is such that the skilled person can introduce genes into plant cells but that generation of a given particular phenotype is unpredictable. Gene expression levels and inheritance are unpredictable (Deroles, SC and Gardner, RC; (1998) Plant Molecular Biology 11: 355-364 ; Dunwell, JM and Paul, EM (1990) Outlook on Agriculture 19, 103-109 ; Finnegan J and McElroy D (1994) Bio/Technology 12: 883-888). Organ-specific gene expression in plants is variable (Van-der-Hoeven C et. al. (1994) Transgenic Research 3: 159-166). Recombinase mediated excision of appropriately flanked DNA sequences is variable and yields chimeric phenotypes having both recombined and unrecombined DNA (Gidoni, D. et al, Supplement to Plant Molecular Biology Reporter 18:2, S 03-40; ISPMB abstracts, June 18-24, 2000). Recent studies (Gidoni, D et al (2001) Euphytica 121: 145-156) of embryonal recombination and germline inheritance of recombined tobacco loci show variable recombination efficiencies (Godini 2001, 146 and 152).

*Amount of Experimentation necessary.* Applicant has provided no guidance on how to predictably eliminate inoperable embodiments from a virtually ad infinitum of possibilities other than by random trial and error, which is excessive experimentation and an undue burden.

Specifically, for any given set of transgenes in a plant, what phenotype is the desired one? For any given set of transgenes, criteria for parameters such as copy number, expression level (RNA or protein) of selectable marker, expression level (or

lack of expression) of genes of interest, expression patterns (or lack of expression) of genes of interest, and stability of transgenes through generations, need to be defined. In both of the prophetic examples for which Applicant includes schematic figures, four sets of transgenes need to be characterized and optimized for at least 5 sets of parameters to find the operable combinations. This represents 500+ combinations to be tested for this one embodiment, and represents excessive experimentation and an undue burden. The enablement of modifying all cellular functions would require an infinite number of variables to be defined and optimized.

In view of the breadth of the claims (modifying all cellular functions), the lack of guidance in the specification, and the unpredictability in the recombinase art, undue trial and error experimentations would be required to enable the invention as commensurate in scope with the claims.

### *Claim Rejections - 35 USC § 103*

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1 – 4, 6, 7, 11-18, 20, 21, and 25 - 37 rejected under 35 U.S.C. 103(a) as being unpatentable over Kilby, Plant Journal 8: 637-652, (1995) in view of Mariani, Nature 347: 737-741(1990), Sancho, J Mol. Biol. 224: 741-747(1992)) and Applicant's own admission.

Kilby teaches introducing into a plant an expression cassette having a first plant promoter operably liked to a first polynucleotide encoding a first polypeptide, where in a recombinase site is present between the first promoter and the first polynucleotide (page 639 figure 2b), introducing into the plant a second expression cassette comprising the first plant promoter inoperably linked to a polynucleotide encoding the first polypeptide, wherein an intervening expression cassette is flanked by recombinase sites and situated between the first polypeptide and the first polypeptide, the intervening DNA encoding a second polypeptide (page 639 figure 2a). Kilby teaches broadly the use of intervening sequences flanked by recombination target sites within an expression cassette. His specific example includes a protein coding sequence as the intervening sequence. Kilby does not teach a plant promoter in the intervening cassette, a nuclease, lox sites, transactivator proteins, barnase, tissue specific promoters, seed coat or tapetal-specific promoters.

Mariani teaches ribonuclease genes controlled by tapetal -specific regulatory sequences (page 738).

Sancho et al teaches a first and second amino acid subsequence of a single functional nuclease (p 741, abstract; p 746).

Applicant admits that various recombinase systems, including the cre/lox recombinase system, were known in the art at the time of filing of the instant application (specification, p. 7). It would have been prima facie obvious to one of ordinary skill in the art to modify Kilby to insert ribonuclease genes controlled by tapetal -specific regulatory sequences as taught by Mariani or a first and second amino acid

subsequence of a single functional nuclease as taught by Sancho for the protein coding sequence of Kilby. It would have been obvious to substitute the Cre/lox system admitted by Applicant to have been known in the art for the FLP/frt system of Kilby. The different coding sequences and recombinase systems are functional equivalents and it would have been obvious to substitute one functional equivalent for another.

Mariani (abstract, p 737, and p741) discusses the value of male sterility genes in the production of hybrid seed and provide motivation to combine male sterility genes with the gene expression and control scenario of Kilby et al.

***Remarks***

7. No claims are allowed.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Georgia L. Helmer whose telephone number is 703-308-7023. The examiner can normally be reached on 8:30 - 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on 703-306-3218. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-4242 for After Final communications. All Technology Sector 1 fax machines are available to receive transmissions 24 hrs/day, 7 days/wk. Please note that the faxing of such papers must conform with the Notice published in the Official Gazette, 1096 OG 30, (November 15, 1989).

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

February 25, 2002
Georgia L. Helmer Ph.D.
Patent Examiner
AU 1638
703-308-7023

AMY J. NELSON, PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600